Risk of Contralateral Testicular Cancer: A Population-based Study of 29 515 U.S. Men

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Background: **Although risk estimates for synchronous and metachronous contralateral testicular cancers vary widely, many clinicians recommend routine biopsy of the contralateral testis for patients diagnosed with unilateral testicular cancer. We evaluated the risk of contralateral testicular cancer and survival in a large population-based cohort of men diagnosed with testicular cancer before age 55 years.** ***Methods:*** **For 29 515 testicular cancer cases reported to the National Cancer Institute's Surveillance, Epidemiology and End Results Program from 1973 through 2001, we estimated the prevalence of synchronous contralateral testicular cancer, the observed-to-expected ratio (O/E) and 15-year cumulative risk of metachronous contralateral testicular cancer, and the 10-year overall survival rate of both synchronous and metachronous contralateral testicular cancer, using the Kaplan–Meier method for the two latter assessments. Age-adjusted multivariable analyses were used to examine risk according to histologic type of the original cancer.** ***Results:*** **A total of 175 men presented with synchronous contralateral testicular cancer; 287 men developed metachronous contralateral testicular cancer (O/E = 12.4 [95% confidence interval {CI} = 11.0 to 13.9]; 15-year cumulative risk = 1.9% [95% CI = 1.7% to 2.1%]). In the multivariable analysis, only nonseminomatous histology of the first testicular cancer was associated with a statistically significantly decreased risk of metachronous contralateral testicular cancer (hazard ratio [HR] = 0.60, 95% confidence interval [CI] = 0.46 to 0.79; *P*<.001). Increasing age at first testicular cancer diagnosis was associated with decreasing risk of nonseminomatous metachronous contralateral testicular cancer (odds ratio = 0.90, 95% CI = 0.86 to 0.94). The 10-year overall survival rate after metachronous contralateral testicular cancer diagnosis was 93% (95% CI = 88% to 96%), and that after synchronous contralateral testicular cancer was 85% (95% CI = 78% to 90%).** ***Conclusions:*** **The low cumulative risk of metachronous contralateral testicular cancer and favorable overall survival of patients diagnosed with metachronous contralateral testicular cancer is in accordance with the current U.S. approach of not performing a biopsy on the contralateral testis. [J Natl Cancer Inst 2005;97:1056–66]**

Increasing numbers of men with unilateral testicular cancer are at risk of developing a subsequent (i.e., metachronous) contralateral testicular cancer, given the high cure rates (approximately 95%) of patients with testicular germ cell tumors and the rising incidence of testicular cancer *(1–9)*. The cumulative risks of metachronous contralateral testicular cancer 20–25 years after initial diagnosis of testicular cancer range from 2.4% to 5.2% *(10–18)*. European men with unilateral testicular cancer have a 12- to 38-fold higher risk of developing a new testicular cancer compared with men from the general population *(13,16,17,19)*. However, many studies *(10–12,14,15)* have reported only the crude percentages of those who develop contralateral testicular cancer, and those estimates were generally lower for men in the United States than for men in Nordic countries (Appendix Table 1). A few large studies *(11,15,17)* have considered simultaneously the influences of age at diagnosis of initial testicular cancer, histology, extent of disease, and treatment on the development of contralateral testicular cancer. Initial diagnosis before the age of 30 years has been reported to be a risk factor for the development of a metachronous contralateral testicular cancer *(17)*. However, data that address survival following the diagnosis of synchronous or metachronous contralateral testicular cancer are sparse.

The primary aim of this study was to evaluate the risk of developing metachronous contralateral testicular cancer in a large, population-based cohort of testicular cancer patients with respect to age at initial diagnosis, histologic type, and treatment and to examine the prevalence of synchronous contralateral testicular cancer in the same cohort. We also estimated long-term overall survival in patients diagnosed with unilateral testicular cancer and contralateral testicular cancer.

Patients and Methods

Patients

This study includes all patients who were diagnosed with testicular germ cell cancer as their first malignancy and whose diagnosis was reported from January 1, 1973, through December 31, 2001, to the following population-based cancer registries that participate in the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) Program (year of registry entry into the SEER Program): Connecticut (1973), Hawaii (1973), Iowa (1973), New Mexico (1973), Utah (1973), San Francisco–Oakland (1973), Detroit (1973), Seattle–Puget Sound (1974), Atlanta (1975), San Jose–Monterey (1988), Los Angeles (1988), rural Georgia (1978), greater California (excluding San Francisco, San Jose–Monterey, and Los Angeles; 1988), Kentucky (1995), Louisiana (1995), and New Jersey (1979).

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Men who had either an extragonadal germ cell tumor or a spermatocytic seminoma were excluded from this study. In addition, because testicular germ cell tumors are typically diagnosed in young and middle-aged men, and because misclassification of testicular lymphoma in older patients *(20)* cannot be excluded in a registry-based series of patients, we limited our study population to patients who were younger than 55 years at the initial diagnosis of testicular cancer.

The registries recorded the following information for each patient: month and year of birth; month and year of last observation; vital status at last observation; and month and year of testicular cancer and contralateral testicular cancer diagnoses.

Laterality

Men whose first testicular cancer was coded as "bilateral" at initial diagnosis or whose second testicular cancer was diagnosed within 2 months of the first diagnosis were considered to have synchronous contralateral testicular cancer. Men who were diagnosed with a contralateral testicular cancer more than 2 months after the first testicular cancer diagnosis were considered to have metachronous contralateral testicular cancer. Thus, we assessed the risk of developing metachronous contralateral testicular cancer only among patients who were diagnosed with contralateral testicular cancer more than 2 months after being diagnosed with unilateral testicular cancer. We evaluated the prevalence of synchronous contralateral testicular cancer among all eligible patients.

Histology

In the SEER Program registries, testicular cancer morphology is coded according to the International Classification of Diseases for Oncology (ICD-0) *(21)*. We grouped the diagnoses into seminomas (codes 9060–9062 and 9064) or nonseminomas (codes 9070–9073, 9080–9085, and 9100–9102).

Extent of Disease

For any solid malignancy, the SEER Program registries record the extent of disease at initial diagnosis as "localized," "regional," "distant metastases," or "unknown," and these categorizations were used in this study. Since 1988, the SEER Program has also collected information on the size (in millimeters) of the testicular tumor as described in the pathology report of the orchiectomy specimen. For men with synchronous contralateral testicular cancer and who had a valid measurement for at least one tumor, and for men with metachronous contralateral testicular cancer in whom the size of the second tumor was evaluable, we calculated the proportion of men who presented with a contralateral testicular cancer of less than 20 mm because such men can be considered for testis-saving surgery *(22,23)*.

Treatment

Unilateral orchiectomy was done in all patients diagnosed with unilateral testicular cancer. Patients who presented with a synchronous contralateral testicular cancer underwent bilateral orchiectomy. Thereafter, patients who were diagnosed with early-stage seminoma (localized at limited regional metastases) had radiotherapy alone *(24)*—usually with testicular lead block shielding *(25)*—or were managed by surveillance *(26)*. Advanced metastatic seminoma was treated by chemotherapy, which was occasionally followed by radiotherapy or surgical removal of residual masses *(27)*. Patients who were diagnosed with early-stage nonseminoma underwent primary retroperitoneal lymph node dissection after orchiectomy *(28)* or were included in a surveillance strategy *(29)*. Adjuvant chemotherapy was given to patients with histologically confirmed metastatic disease; an alternative was abdominopelvic radiotherapy *(30)*. Treatment of metastatic nonseminoma consisted of initial chemotherapy followed by surgery and/or (although rarely) radiotherapy *(27)*. In the early 1970s, chemotherapy for testicular cancer consisted mainly of cyclophosphamide, chlorambucil, methotrexate, and actinomycin D; subsequently, this regimen was replaced by combinations of bleomycin, vinblastine, and doxorubicin *(24,28)*. After 1975, cisplatin-based combination therapies were increasingly used. These therapies commonly included cisplatin, vinblastine, and bleomycin *(31)* or cisplatin, etoposide, and bleomycin *(32)*.

SEER Program registries collected information only for the initial course of treatment applied after a diagnosis of testicular cancer or metachronous contralateral testicular cancer. No details were available about the type or doses of chemotherapy or radiotherapy received or about the use of salvage treatment. Initial postorchiectomy treatment, regardless of any concomitant surgery or hormonal therapy, was classified according to the following categories: 1) surgery alone; 2) radiotherapy alone; 3) chemotherapy alone; 4) radiotherapy and chemotherapy; and 5) other/not specified. We further stratified patients according to whether they received treatment with chemotherapy: no chemotherapy (initial treatment categories 1 and 2); any chemotherapy (initial treatment categories 3 and 4); and other/not specified (initial treatment category 5).

Statistical Analysis

We used SPSS software (version 12.0; SPSS, Chicago, IL) to calculate medians and ranges and to conduct Kruskal–Wallis and Wilcoxon tests for comparisons. Categorical variables were compared by using the chi-square test. Latency was defined as the interval between the date of the first diagnosis of testicular cancer and the date of the diagnosis of metachronous contralateral testicular cancer.

To calculate the risk of metachronous contralateral testicular cancer, person-years at risk were assembled by age at diagnosis and by calendar year periods beginning 2 months after the diagnosis of unilateral testicular cancer to the date of diagnosis of metachronous contralateral testicular cancer, age 55 years, date of death, or end of the study (December 31, 2001), whichever occurred first. Of the 28 045 men who had more than 2 months of observation time, 43 men reached the age of 55 years within 3 months of their initial diagnosis and therefore did not contribute person-years to the analysis. Thus, estimates of metachronous contralateral testicular cancer risk were based on the remaining 28 002 (99.8%) patients. We estimated the expected number of testicular cancers by using SEER Program data to calculate testicular cancer incidence rates by 5-year age groups and by 5-year calendar year intervals; these rates were then multiplied by the number of accumulated person-years. We then added the total number of observed metachronous contralateral testicular cancers and the total number of expected testicular cancers, and the relative risk for each interval was defined as the ratio of the number of observed cases to the number of expected cases (O/E).

We used the Kaplan–Meier method *(33)* to estimate the overall cumulative probability of developing a metachronous contralateral testicular cancer over time and the log-rank test *(34)* to test for differences in cumulative risks. For the analysis of cumulative risk, the observation time started 2 months after the date of diagnosis of the first testicular cancer and ended on the date the patient reached age 55 years, died, or was lost to follow-up or diagnosed with metachronous contralateral testicular cancer, whichever occurred first. Two patients who developed a metachronous contralateral non–germ cell cancer were censored at the date of the second diagnosis of testicular cancer.

To evaluate associations between features of the primary testicular cancer and the risk of metachronous contralateral testicular cancer, we performed Cox proportional hazards analysis to obtain hazard ratios (HRs) and 95% confidence intervals (CIs). The proportional hazards assumption was assessed using the method of Grambsch and Therneau *(35)* and was found to hold for all the fitted models. We used the Wald statistic to assess the statistical significance of the associations. We used logistic regression to examine which features of the primary testicular cancer were associated with the histology of the metachronous contralateral testicular cancer (seminoma versus nonseminoma). All statistical tests were two-sided, and $P<.05$ was considered statistically significant. We used Splus statistical software to perform Cox regression analysis and the logistic regression (Mathsoft, Seattle, WA).

We used the Kaplan–Meier method *(33)* to assess overall survival among patients with synchronous contralateral testicular cancer and among patients initially diagnosed with unilateral testicular cancer, stratifying by extent of disease in the latter group. The observation time started with the date of diagnosis of the first testicular cancer and ended with the date of the patient's death, the date the patient was lost to follow-up, or December 31, 2001, whichever occurred first. The log-rank test *(34)* was used to evaluate differences between the survival curves. In a separate analysis, we estimated overall survival in patients with metachronous contralateral testicular cancer from the date of metachronous contralateral testicular cancer diagnosis to the date of the patient's death, the date the patient was lost to follow-up, or December 31, 2001, whichever occurred first. Using the age-specific death rates in 2001 for the white male U.S. population *(36)*, we also estimated the expected survival in the white U.S. population. Comparisons between the patients with unilateral testicular cancer and those with synchronous contralateral testicular cancer concentrated on 10-year survival because of the limited information on survival beyond 10 years for men with synchronous contralateral testicular cancer.

Results

In the SEER Program registries examined, a total of 29 515 men were diagnosed with testicular cancer before age 55 years, including 175 men (0.6%) who presented with synchronous contralateral testicular cancer (Table 1). Of the remaining 29 340 patients with unilateral testicular cancer, 28 045 men had a unilateral testicular cancer and a follow-up period of greater than 2 months. Among the 20 866 patients with unilateral testicular cancer whose extent of disease was known, 78% of the 11 724 seminoma patients and 55% of the 9142 nonseminoma patients had localized disease. Among the 27 255 patients whose initial treatment was recorded, 6% of the 15 315 seminoma patients and 28% of the 11 940 nonseminoma patients had chemotherapy.

Among the 175 men who were diagnosed with synchronous contralateral testicular cancer, those with at least one nonseminomatous testicular cancer were younger than those with bilateral seminoma (31 years versus 37 years; $P<.001$, Wilcoxon test) (Table 2). Among patients whose extent of disease was known, 45% of those with synchronous contralateral testicular cancer had regional or distant disease (61 of 135), compared with only 32% of those with unilateral testicular cancer (6705 of 20 866) ($P = .001$, chi-square test). For 55 (54%) of 101 patients with synchronous contralateral testicular cancer and for whom the size of at least one tumor was recorded, at least one tumor measured less than 20 mm in diameter.

Metachronous Contralateral Testicular Cancer

After a median latency of 63 months (range = 3–223 months), metachronous contralateral testicular cancer was diagnosed in 173 of the 15 640 men who were previously diagnosed with a seminoma and in 114 of the 12 230 men who were previously diagnosed with a nonseminoma (Table 3). Of these second tumors, 191 were seminomas and 96 were nonseminomas (Table 3). Only one (1%) of the 173 men with a seminoma at first diagnosis had received chemotherapy as initial treatment, compared with 38 (33%) of 114 men with a nonseminoma at first diagnosis. In all 39 of the patients, the metachronous contralateral testicular cancer developed after completion of the initial chemotherapy. Of the 244 patients with metachronous contralateral testicular cancer for whom extent of disease was known, 207 (85%) had localized disease. Only 27 patients (9%) with metachronous contralateral testicular cancer received chemotherapy. Of the 190 metachronous contralateral testicular cancers of known size, 69 (36%) were less than 20 mm in diameter.

In univariate analyses of the 28 002 patients with unilateral testicular cancer, treatment of the initial unilateral testicular cancer with chemotherapy, an initial unilateral testicular cancer with nonseminomatous histology, and the presence of distant metastases were each associated with a decreased risk of a metachronous contralateral testicular cancer (Table 4). In the multivariable analysis, however, only nonseminomatous histology of the first testicular cancer was associated with statistically significantly decreased risk of metachronous contralateral testicular cancer (hazard ratio [HR] = 0.60, 95% confidence interval [CI] = 0.46 to 0.79; $P<.001$). We also examined the risks of developing nonseminomatous and seminomatous tumors by carrying out logistic regression analysis among patients who developed a metachronous contralateral tumor (Table 5). In univariate analyses with age as a continuous variable, older age at first testicular cancer diagnosis was associated with a decreased risk of nonseminomatous versus seminomatous metachronous contralateral testicular cancer (odds ratio [OR] = 0.90, 95% CI = 0.86 to 0.94), whereas the risk of nonseminomatous metachronous contralateral testicular cancer was higher in men with an initial nonseminomatous testicular cancer than in men with an initial seminomatous testicular cancer (OR = 1.66, 95% CI = 1.01 to 2.74) and was also higher in men who were initially treated with chemotherapy than in men who received no chemotherapy (OR = 2.31, 95% CI = 1.17 to 4.58). In multivariable analyses, older age at first testicular cancer diagnosis remained statistically significantly associated with a decreased risk of

Table 1. Characteristics of patients with testicular germ cell tumors reported to the Surveillance, Epidemiology, and End Results Program (1973–2001)*

	No. of patients (%)	Median age at diagnosis, y (range)	No. of person-years†	No. of patients diagnosed with Met-CTC
All patients	29 515 (100)	32 (0–54)	NA	NA
Synchronous CTC	175 (0.6)	34 (18–54)	NA	NA
Race‡				
White	26 361 (94)	32 (0–54)	203 516	277
Other	1684 (6)	31 (0–54)	11 556	10
Year of diagnosis				
1973–1982	3920 (14)	29 (0–54)	57 924	68
1983–1992	10 097 (36)	31 (0–54)	105 141	135
1993–2001	14 028 (50)	33 (0–54)	52 007	84
Age at diagnosis, y				
<20	1545 (6)	18 (0–19)	12 633	25
20–29	9350 (33)	26 (20–29)	83 620	134
30–39	11 157 (40)	34 (30–39)	87 792	104
≥40	5993 (21)	44 (40–54)	31 026	24
Histology				
Seminoma	15 728 (56)	35 (0–54)	115 866	173
Nonseminoma	12 317 (44)	28 (0–54)	99 206	114
Size of testicular tumor, mm				
<20	2157 (8)	31 (0–54)	12 472	21
20–49	7626 (27)	32 (0–54)	45 881	80
50–99	4014 (14)	33 (0–54)	21 417	30
Unknown	14 248 (51)	31 (0–54)	135 303	156
Extent of disease				
Seminoma				
Localized	9153 (58)	35 (5–54)	64 143	106
Regional	1872 (12)	36 (1–54)	13 711	21
Distant	699 (4)	36 (14–54)	4109	2
Unknown	4004 (25)	34 (0–54)	33 903	44
Nonseminoma				
Localized	5008 (41)	28 (0–54)	40 579	50
Regional	2379 (19)	28 (0–54)	20 391	28
Distant	1755 (14)	27 (0–54)	10 571	8
Unknown	3175 (26)	28 (0–54)	27 664	28
Treatment§				
Seminoma				
Surgery alone	8164 (52)	35 (0–54)	37 831	52
Radiotherapy alone	6299 (40)	35 (12–54)	66 654	116
Chemotherapy alone	717 (5)	35 (14–54)	5841	1
Radiotherapy and chemotherapy	135 (1)	35 (16–53)	1273	0
Other/not specified	413 (3)	34 (12–54)	4268	4
Nonseminoma				
Surgery alone	8420 (68)	28 (0–54)	59 346	67
Radiotherapy alone	186 (2)	28 (17–54)	2426	6
Chemotherapy alone	3157 (26)	27 (0–54)	31 745	39
Radiotherapy and chemotherapy	177 (1)	26 (13–52)	1484	1
Other/not specified	377 (3)	26 (0–53)	4205	1

*CTC = contralateral testicular cancer; Obs. = observation; Met-CTC = metachronous contralateral testicular cancer; NA = not applicable.

†Person-years given only for patients with an observation time for contralateral testicular cancer of more than 2 months after the date of diagnosis of the first testicular cancer, calculated to the date of diagnosis of metachronous contralateral testicular cancer, the date of death, the date the patient turned 55 years old, or December 31, 2001, whichever occurred first. The 43 patients who had zero person-years were excluded from analyses of metachronous contralateral testicular cancer.

‡The remainder of the table includes the 28 045 patients with unilateral testicular cancer and follow-up for more than 2 months after unilateral testicular cancer diagnosis.

§Reflects only the initial course of treatment as reported to Surveillance, Epidemiology, and End Results Program registries. Data with regard to subsequent therapy were not collected.

nonseminomatous versus seminomatous metachronous contralateral testicular cancer (OR = 0.90, 95% CI = 0.86 to 0.94). However, in the multivariable analysis, initial nonseminomatous histology (OR = 0.73, 95% CI = 0.38 to 1.38) and initial chemotherapy (OR = 2.00, 95% CI = 0.83 to 4.83) were associated with lower risks of metachronous contralateral nonseminoma than were observed in the univariate analyses. This result can be explained by the strong association we observed between histology and initial treatment: Among patients with a metachronous contralateral tumor for whom treatment was known, one (1%) of 169 seminoma patients and 38 (34%) of 113 nonseminoma patients had initially received chemotherapy ($P<.001$, chi-square test). Thus the apparent association with histology in the univariate analysis was due largely to the different use of chemotherapy in the seminoma versus nonseminoma patients.

The 15-year cumulative risk of developing a metachronous contralateral testicular cancer was 1.9% (95% CI = 1.7% to 2.1%) (Fig. 1). The risks of developing metachronous contralateral testicular cancer according to age at first testicular cancer diagnosis (younger than 30 years versus 30 years or older) and histology of first testicular cancer (seminoma versus

Table 2. Characteristics of 175 patients with synchronous contralateral testicular cancer reported to the Surveillance, Epidemiology, and End Results Program (1973–2001)

Characteristics	No. of patients (%)	Median age at diagnosis, y (range)
Histology		
Seminoma/Seminoma	88 (50)	37 (19–53)
Seminoma/Nonseminoma	59 (34)	32 (22–46)
Nonseminoma/Nonseminoma	28 (16)	31 (19–53)
Extent of disease		
Localized	74 (42)	35 (22–53)
Regional	37 (21)	35 (22–54)
Distant	24 (14)	31 (19–53)
Unknown	40 (23)	34 (18–52)
Treatment		
No chemotherapy	136 (78)	35 (18–53)
Any chemotherapy	36 (21)	34 (22–54)
Other/not specified	3 (2)	34 (33–36)
Smallest diameter of either tumor, mm		
<20	55 (31)	33 (22–50)
20–49	36 (21)	38 (22–49)
50–99	10 (6)	39 (25–53)
Unknown	74 (42)	33 (18–54)

nonseminoma) are shown in Figure 2. Men who were younger than 30 years at diagnosis with a seminomatous unilateral testicular cancer had the highest 15-year cumulative risk of developing metachronous contralateral testicular cancer (3.1%, 95% CI = 2.4% to 4.0%), whereas men who were 30 years or older at diagnosis with a nonseminomatous unilateral testicular cancer had the lowest 15-year cumulative risk of developing metachronous contralateral testicular cancer (1.2%, 95% CI = 0.8% to 1.8%).

The overall risk of metachronous contralateral testicular cancer among the 28 002 patients with unilateral testicular cancer was more than 12-fold higher than the general population risk (O/E = 12.4, 95% CI = 11.0 to 13.9). For these patients, the risk of metachronous contralateral testicular cancer remained statistically significantly elevated relative to the general population during the first 10 years after the initial testicular cancer diagnosis, although the magnitude of the elevation decreased over time [0–4 years after diagnosis: O/E = 13.8 (95% CI = 11.7 to 16.1); 5–9 years after diagnosis: O/E = 12.8 (95% CI = 10.3 to 15.7); 10–14 years after diagnosis: O/E = 10.2 (95% CI = 6.9 to 14.4); ≥15 years after diagnosis: O/E = 3.0 (95% CI = 0.8 to 7.6). A similar pattern of decreasing observed-to-expected ratios after 10 years was observed among the subgroup of patients who received radiotherapy only as initial treatment (data not shown).

Overall Survival

The 10-year overall survival rates for all initially unilateral testicular cancer patients with localized disease, regional disease, and distant metastases were 95% (95% CI = 94.5% to 95.4%), 90% (95% CI = 88.8% to 91.0%), and 65% (95% CI = 63.0% to 67.1%), respectively (Fig. 3). The 10-year overall survival rate for all patients with synchronous contralateral testicular cancer was 85% (95% CI = 78% to 90%).

Among the 287 patients who developed a metachronous contralateral testicular cancer, the 10-year survival rate following the metachronous contralateral testicular cancer diagnosis was 93% (95% CI = 88% to 96%). Testicular cancer was the reported cause of death for only one of these 287 patients with metachronous contralateral testicular cancer. Among these 287 patients, distant metastases at initial testicular cancer diagnosis (HR = 8.05; 95% CI = 1.44 to 45.04) and regional disease at the time of the metachronous contralateral testicular cancer diagnosis (HR = 4.27; 95% CI = 1.01 to 17.96) were associated with statistically significantly decreased survival. A time-dependent covariate analysis compared the risk of death among men with metachronous contralateral testicular cancer with that among men without metachronous contralateral testicular cancer during the same time interval after the date of the initial unilateral testicular cancer diagnosis. The development of metachronous contralateral testicular cancer did not increase the mortality risk beyond that associated with unilateral testicular cancer, even after adjustment for age at diagnosis of the primary testicular cancer; the hazard of death was lower in the men with metachronous contralateral testicular cancer than in those without metachronous contralateral testicular cancer, but the difference was not statistically significant (HR = 0.76; 95% CI = 0.45 to 1.26).

Discussion

In this large, population-based series of nearly 30 000 patients with unilateral testicular cancer, we show for the first time that U.S. testicular cancer patients have a 12.4-fold increased risk of developing a metachronous contralateral testicular cancer compared with the general population. This increased risk was highest during the first 5 years after orchiectomy and decreased thereafter. The 15-year cumulative risk of developing a metachronous contralateral testicular cancer was 1.9%. Other new findings include our observation that, after adjustment for age, patients with seminomatous unilateral testicular cancer had a higher risk of metachronous contralateral testicular cancer than patients with a nonseminomatous unilateral testicular cancer. Older age at the time of the first testicular cancer diagnosis was associated with a reduced risk of nonseminomatous metachronous contralateral testicular cancer as compared to seminomatous histology. In addition, this study is the first, to our knowledge, to document that development of a metachronous contralateral testicular cancer is not associated with a decrease in overall survival as compared to patients without a metachronous testicular cancer.

The development of bilateral testicular cancer finds some etiologic explanation in the most frequently accepted hypothesis about germ cell carcinogenesis. The malignant process is believed to start during the 7th through 9th weeks of embryonal life *(37)*. Environmental factors are believed to cause changes in the male embryo's primordial cells, from which the testes later develop. These prenatal influences are thought to be related to the initiation of carcinoma in situ and the subsequent development of invasive testicular cancer *(37)*. Whether carcinogenesis occurs in one or both testes depends on the distribution of cells that were exposed to these prenatal influences. Cancer development is believed to start earlier and have a higher growth rate in men with nonseminoma *(38)* than in men with seminoma, which explains the younger age of nonseminoma patients at first presentation. In some men, the development of testicular cancer is also genetically determined, as indicated by the occurrence of familial testicular cancer *(39,40)*.

Table 3. Characteristics of 287 patients who developed a metachronous contralateral testicular cancer

	Metachronous contralateral testicular cancer			
	Seminoma	Nonseminoma	Total	*P**
Number of patients (%)	191 (67)	96 (33)	287 (100)	
Median latency, mo (range)	67 (3–223)	55 (4–158)	63 (3–223)	.06†
Characteristics related to initial unilateral testicular cancer				
Histology, No. (%)				
Seminoma	123 (64)	50 (52)	173 (60)	
Nonseminoma	68 (36)	46 (48)	114 (40)	.044
Median age at diagnosis, y (range)	31 (17–49)	26 (15–41)	29 (15–49)	<.001†
Age at diagnosis, No. (%)				
<30	88 (46)	72 (75)	160 (58)	
≥30	103 (54)	24 (25)	127 (42)	<.001
Extent of disease, No. (%)				
Localized	108 (57)	48 (50)	156 (54)	
Regional	31 (16)	18 (19)	49 (17)	
Distant	6 (3)	4 (4)	10 (3)	
Unknown	46 (24)	26 (27)	72 (25)	.50
Treatment, No. (%)				
Seminoma				
No chemotherapy	118 (96)	50 (100)	168 (97)	
Any chemotherapy	1 (1)	0	1 (1)	
Other/not specified	4 (3)	0	4 (2)	.014
Nonseminoma				
No chemotherapy	49 (72)	26 (57)	75 (66)	
Any chemotherapy	18 (27)	20 (44)	38 (33)	
Other/not specified	1 (2)	0	1 (1)	.131
Characteristics at the time of metachronous contralateral testicular cancer diagnosis				
Median age at diagnosis, y (range)	36 (19–55)	31 (18–47)	35 (18–55)	<.001†
Extent of disease, No. (%)				
Localized	140 (73)	67 (70)	207 (72)	
Regional	17 (9)	14 (15)	31 (11)	
Distant	2 (1)	4 (4)	6 (2)	
Unknown	32 (17)	11 (12)	43 (15)	.103
Treatment, No. (%)				
Surgery only	140 (73)	76 (79)	216 (76)	
Radiation	44 (23)	0 (0)	44 (15)	
Any chemotherapy	7 (4)	20 (21)	27 (9)	<.001
Diameter of metachronous contralateral testicular tumor, No. (%)				
<20 mm	47 (25)	22 (23)	69 (24)	
20–49 mm	59 (31)	35 (37)	94 (33)	
≥50 mm	20 (11)	7 (7)	27 (9)	.71
Unknown	65 (34)	32 (33)	97 (34)	

*Two-sided chi square test, except where indicated.

†Two-sided Student's *t* test.

This hypothesis provides a partial explanation for the occurrence of bilateral testicular cancer we observed in patients diagnosed with testicular cancer. In 2%–5% of patients with testicular cancer, the germinative epithelium in both testes seems to contain cell clones with pre-malignant changes. Importantly, our finding that observed-to-expected ratios for metachronous contralateral testicular cancer started declining by 5 years after diagnosis, even among patients who received radiotherapy as initial treatment, indicates that the elevated risk of metachronous contralateral testicular cancer was unrelated to radiotherapy. These results contrast with the increased risks of the development of non–germ cell cancers among men treated for testicular cancer *(41)*. Prenatal predisposition to bilateral germ cell malignancy also provides a reasonable explanation for our observations, and those of others *(11,15,17)*, that young adult age at first testicular cancer diagnosis is a risk factor for developing a metachronous contralateral testicular cancer. The fact that the nonseminoma patients have a younger median age at diagnosis than seminoma patients supports the hypothesis that the carcinogenic process associated with the development of nonseminomas is faster and/or more intense than that associated with the development of seminomas.

The overall observed-to-expected ratio (12.4) and 15-year cumulative incidence risk (1.9%) of metachronous contralateral testicular cancer estimated in this study are lower than the estimates reported by most European studies with comparable information *(13,16,17)*. The observed-to-expected ratio we report is, however, in line with the 11- to 12-fold increased risk of metachronous contralateral testicular tumors that has been reported among Swedish patients *(18)*. There are several possible explanations for the discrepant results with the other European studies. First, European analyses of subsequent testicular cell cancer after a first germ cell cancer diagnosis often include patients with extragonadal germ cell cancer who have a particularly high incidence of metachronous testicular cancer *(17,42)*. Second, in some studies, the reported incidence estimates included patients with synchronous contralateral testicular cancer and patients with metachronous contralateral testicular

Table 4. Cox regression analysis of clinical risk factors for the development of metachronous contralateral testicular cancer (Met-CTC)*

Characteristics of initial unilateral testicular cancer	No. of patients diagnosed with Met-CTC	Univariate HR (95% CI)	Multivariable† HR (95% CI)
Histology			
Seminoma	173	1.00 (referent)	1.00 (referent)
Nonseminoma	114	0.56 (0.43 to 0.73)	0.60 (0.46 to 0.79)
Treatment			
No chemotherapy	243	1.00 (referent)	1.00 (referent)
Any chemotherapy	39	0.66 (0.47 to 0.93)	0.86 (0.58 to 1.28)
Other/not specified	5	0.42 (0.18 to 1.01)	0.50 (0.20 to 1.24)
Extent of disease			
Localized	156	1.00 (referent)	1.00 (referent)
Regional	49	0.95 (0.69 to 1.31)	1.10 (0.78 to 1.55)
Distant	10	0.43 (0.23 to 0.81)	0.54 (0.28 to 1.08)
Unknown	72	0.73 (0.55 to 0.97)	0.81 (0.61 to 1.08)

*Analysis restricted to the 28 002 patients who were younger than 55 years at initial diagnosis. Follow-up was truncated at age 55 years. Age was adjusted as a linear effect in both the univariate and multivariable analyses. HR = hazard ratio; CI = confidence interval.

†Age at initial diagnosis, histology, initial treatment, and extent of disease were included in the model.

cancer *(10,11,15,17)*. Third, as discussed by Tabernero et al. *(43)*, the risk of developing a metachronous contralateral testicular cancer may reflect unexplained variations in testicular cancer rates between countries. For example, in SEER Program registries, the incidence of testicular cancer among white men was 5.6 per 100 000 from 1993 through 1997 *(44)*. This rate is lower than published rates for Norway (8.2 per 100 000) and Denmark (9.9 per 100 000) but comparable to the Swedish rate (5.0 per 100 000) *(44)*. Fourth, and probably most important, most published studies included many patients who were treated before cisplatin-based chemotherapy was introduced in the 1970s, whereas most patients with metastases reported to the SEER Program from 1973 through 2001 probably received cisplatin-based chemotherapy as standard therapy. Because cisplatin-based chemotherapy has been associated with decreased risk and delayed development of a metachronous contralateral testicular cancer *(13,45)*, overall risk estimates will differ according to the use of this treatment regimen. In addition, the use of cisplatin-based chemotherapy series by patients in our study may have decreased the risk of metachronous contralateral cancer among nonseminoma patients. For example, studies that included patients diagnosed before the cisplatin era *(16,17)* have reported that patients initially diagnosed with nonseminoma had increased risks of metachronous contralateral testicular cancer compared with patients initially diagnosed with seminoma. In general, nonseminoma patients are more likely to receive cisplatin than are the seminoma patients. The use of chemotherapy was, for example, approximately five times higher in our patients with an initial nonseminoma than in those with seminoma.

Our findings on incidence are in agreement with those reported by Theodore et al. for patients treated between 1979 and 2001 *(15)*. These authors reported crude incidence rates of metachronous contralateral testicular cancer of 3.2% and 1.4% for men with seminoma and with nonseminoma, respectively. It should be noted that differences in risk estimates of metachronous contralateral tumors between the two main treatment categories for our study subjects (no chemotherapy versus any chemotherapy) are likely larger than shown because of possible misclassification introduced by the fact that our records include data on only the initial course of therapy. Chemotherapy is known to be underreported in the SEER Program *(46)*; thus, some

Table 5. Logistic regression analysis of the risk of nonseminoma versus seminoma in patients with metachronous contralateral testicular cancer (Met-CTC)*

Characteristics of initial unilateral testicular cancer	Met-CTC histology†		Univariate	Multivariable‡
	Seminoma	Nonseminoma	OR (95% CI)	OR (95% CI)
Age at diagnosis, y			0.90 (0.86 to 0.94)	0.90 (0.86 to 0.94)
Histology				
Seminoma	123	50	1.00 (referent)	1.00 (referent)
Nonseminoma	68	46	1.66 (1.01 to 2.74)	0.73 (0.38 to 1.38)
Treatment§				
No chemotherapy	167	76	1.00 (referent)	1.00 (referent)
Any chemotherapy	19	20	2.31 (1.17 to 4.58)	2.00 (0.83 to 4.83)
Extent of disease				
Localized	108	48	1.00 (referent)	1.00 (referent)
Regional	31	18	1.31 (0.67 to 2.56)	0.90 (0.41 to 1.98)
Distant	6	4	1.50 (0.41 to 5.56)	0.97 (0.22 to 4.24)
Unknown	46	26	1.27 (0.71 to 2.29)	1.43 (0.76 to 2.69)

*Analysis restricted to 287 patients who were younger than 55 years at initial diagnosis. Follow-up was truncated at age 55 years. Age was adjusted as a linear effect in the univariate and multivariable analyses. OR = odds ratio; CI = confidence interval.

†Number of patients with seminomatous or nonseminomatous metachronous contralateral testicular cancer.

‡In the multivariable analysis, age, histology, treatment, and extent of disease were included in the model.

§Five patients for whom the treatment was unknown were excluded from this analysis.

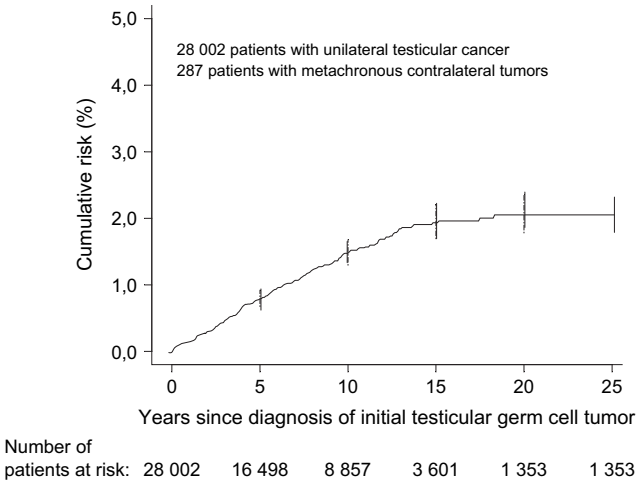

Fig. 1. Cumulative risk of developing a metachronous contralateral testicular cancer (Met-CTC). **Vertical lines** indicate 95% confidence intervals.

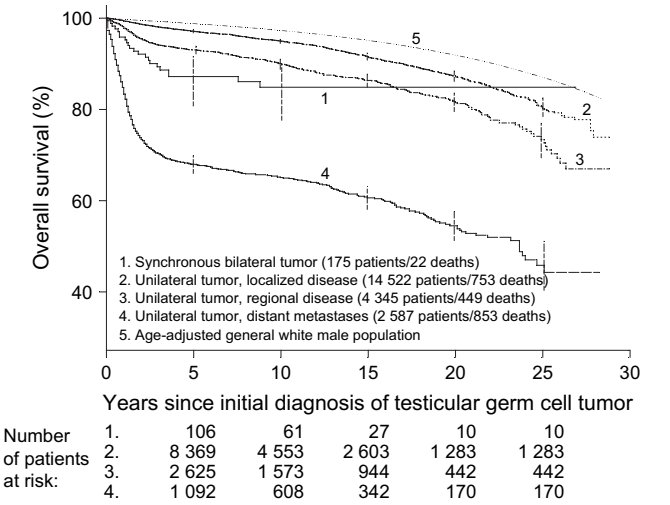

Fig. 3. Overall survival of patients who initially presented with unilateral or synchronous bilateral testicular germ cell tumors, stratified by extent of the disease at diagnosis and compared with survival of the age-matched general white male U.S. population *(36)*. **Vertical lines** indicate pointwise 95% confidence intervals.

patients whose initial treatment was designated as "surgery only" or "radiotherapy only" likely also received chemotherapy. Moreover, the SEER Program registries do not collect data on salvage treatment. For example, nonseminoma patients whose initial treatment was designated as surgery only may have later received chemotherapy as adjuvant or salvage treatment. Bearing in mind this potential misclassification, our finding that these patients had a reduced risk of developing a metachronous testicular cancer after chemotherapy, although statistically significant only in the univariate analysis, supports more limited observations that suggest that modern chemotherapy is associated with a decrease in the occurrence of metachronous contralateral testicular cancer *(45)*. The fact that 39 patients in our study developed metachronous contralateral testicular cancer after completing chemotherapy also confirms published observations that cisplatin-based chemotherapy does not completely eliminate this risk *(47–49)*. A potential dose–response relationship between cisplatin and eradication of germ cell carcinoma in situ should be investigated in future clinical studies.

The need to perform a routine biopsy of the contralateral testis in patients with newly diagnosed unilateral testicular cancer is a matter of ongoing discussion. On the basis of a 5.4% prevalence of carcinoma in situ in the contralateral testis *(50)* and a 5%–6% overall cumulative risk of metachronous contralateral testicular cancer in Danish testicular cancer patients *(51)*, some European investigators advise that all testicular cancer patients have a biopsy of the contralateral testis, followed by treatment of any carcinoma in situ *(51–53)*. Heidenreich and Moul *(54)* recommend this approach only for high-risk patients. Some American investigators have not been in favor of routine biopsy of the contralateral testis *(55)*, a view that likely reflects the published low crude percentages of contralateral testicular cancer patients in U.S. studies (Appendix Table 1).

Our results suggest that, given current treatment practices in the United States, patients with unilateral testicular cancer are at increased risk of developing metachronous contralateral testicular cancer. Patients with seminomatous tumors had a statistically significantly higher probability of developing metachronous contralateral testicular cancer than patients with a nonseminoma, although the risk in both groups decreased with increasing age at first testicular cancer diagnosis. We therefore believe that clinicians should encourage all unilateral testicular cancer patients, especially those not receiving chemotherapy, to perform regular self-examination and, possibly, undergo regular testicular ultrasonography *(56)*. The aim of this approach is to detect a nonmetastatic metachronous contralateral testicular cancer while the primary tumor is still small enough to perform testis-sparing surgery and thus avoid problems associated with androgen substitution after bilateral orchiectomy *(57)*. Our observations on tumor size in the contralateral testis indicate that testis-sparing surgery might have been possible in at least one-third of SEER Program patients diagnosed with contralateral testicular cancer. This fraction can probably be increased with improved surveillance of men with unilateral testicular cancer, particularly the high-risk patients. Finally, a testicular biopsy followed by individual

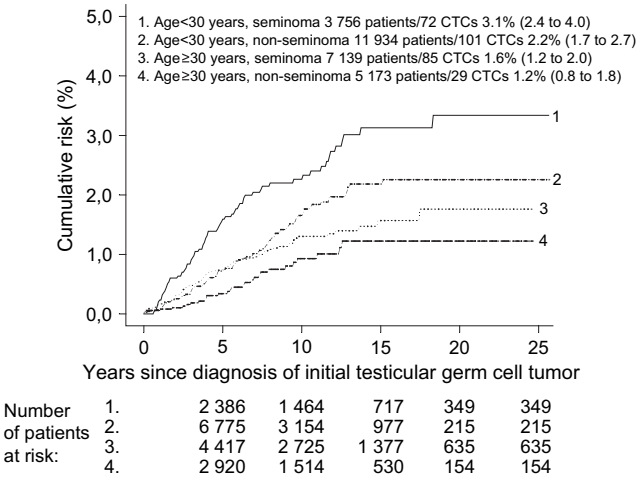

Fig. 2. Cumulative risk of developing a metachronous contralateral testicular cancer (Met-CTC) in 28 002 patients with unilateral testicular germ cell tumor according to risk groups defined by age at initial diagnosis and initial histology. For each group, the number of patients with unilateral testicular cancer and the number of patients who developed a metachronous contralateral testicular cancer is shown together, followed by the 15-year cumulative risk (95% confidence interval).

counseling and/or treatment of carcinoma in situ may be justified for high-risk patients, especially those with a history of testicular maldescent, infertility, or testicular atrophy or a family history of testicular cancer *(58)*. Clinicians and patients should, however, be aware that the overall risk of developing a metachronous contralateral testicular cancer is low, given that the overall 15-year cumulative incidence in our population was less than 2%.

Many investigators have emphasized the good prognosis of patients with metachronous contralateral testicular cancer *(11,12,15)*, but the published reports are based on small numbers and usually lack confirmatory statistical analyses. For example, Géczi et al. *(14)* reported a 93% 5-year survival rate for 53 patients after diagnosis with metachronous contralateral testicular cancer. This rate is comparable to the 10-year overall survival rate of 93% we report for all 287 patients with metachronous contralateral testicular cancer in our study. Our results should be viewed within the context of the limited initial use of radiotherapy or chemotherapy after the diagnosis of metachronous contralateral testicular cancer, given that most patients presented with localized disease. Furthermore, our observations indicate that a diagnosis of metachronous contralateral testicular cancer did not compromise 10-year overall survival compared with that of patients diagnosed with unilateral testicular cancer. However, the statistically significant association between regional metastases and mortality underscores the importance of early diagnosis of metachronous contralateral testicular cancer.

The major strength of this population-based study was its large size, which enabled us to perform statistical analyses of substantial numbers of synchronous contralateral testicular cancer and metachronous contralateral testicular cancer cases. Furthermore, the current study population was not subject to selection bias that may affect populations derived from referral centers. In addition, the likelihood of misclassification based on incorrect histology was greatly reduced because we restricted our analysis to patients who were younger than 55 years at testicular cancer diagnosis.

Limitations of our study include the lack of detailed information about any treatment received after initial treatment, incomplete information on adjuvant chemotherapy, and the lack of data on salvage treatment. Another limitation was the lack of information regarding additional clinical risk factors for developing a metachronous contralateral testicular cancer, such as history of testicular maldescent, infertility, or testicular atrophy. In addition, underreporting of metachronous contralateral testicular cancers, particularly those diagnosed in the youngest men who may migrate from registry catchment areas, may be a problem in the SEER Program registries.

In conclusion, our findings—that U.S. patients with unilateral testicular cancer have a modest 15-year cumulative risk (1.9%) of metachronous contralateral testicular cancer and their high long-term survival—provide support for continuing the usual clinical practice of not subjecting the contralateral testis to routine biopsy. Our results also provide indirect evidence that cisplatin-based chemotherapy may reduce, but not eliminate, the risk of developing a metachronous contralateral testicular cancer.

Appendix Table 1. Literature review of selected studies*

Country/region and first author, year published (reference)	Study period	Institution	No. of patients	No. of patients diagnosed with Syn-CTC (%)	No. of patients diagnosed with Met-CTC (%)†	O/E (95% CI) of any contralateral testicular tumor	Cumulative risk of any testicular tumor (95% CI)	Interval: Incidence of testicular cancer‡
United States								
Fosså, this study	1973–2001	SEER Program	29 515	175 (0.6)	287 (1.0)	124 (110 to 13.9)	15-year: 1.9% (1.7% to 2.1%)	1973–1997: 3.8–5.5§
Coogan, 1998 *(10)*	Not given	Indiana University	2088	5 (0.2)	16 (0.8)	NA	NA	Not given
Che, 2002 *(11)*	1978–1999	M. D. Anderson	2431	4 (0.2)	20 (0.8)	NA	NA	1978–1997:4.3–5.6
Holzbeierlein, 2003 *(12)*	1950–2001	Sloan Kettering	3984	10 (0.3)	48 (1.2)	NA	NA	1973–1997:3.8–5.6
The Netherlands								
Van Leeuwen, 1993 *(13)*	1971–1985	Committee of Testicular tumors	1909(1-y survivors)	4 (0.2)	20 (1.0)	35.7 (21.8 to 55.2)	15-year: 2.4% (1.4% to 3.9%)	1971–1985:3.1
Hungary								
Geczi, 2003 *(14)*	1988–1998	National Institute of Oncology	2386	19 (0.8)	53 (2.2)	NA	NA	1983–1987:2.7
France								
Theodore, 2004 *(15)*	1979–2002	Institut Gustave Roussy	2383	14 (0.6)	31 (1.3)	NA	NA	1993–1997:7.9
Denmark								
Østerlind, 1991 *(16)*	1960–1979	National Cancer Registry	2850	5 (0.2)	68 (2.4)	24.8 (19.3 to 31.4)	20-year: 5.2% (3.7% to 6.7%)	1958–1997:4.6–9.9
Norway								
Wanderaas, 1997 *(17)*	1953–1990	Norwegian Radium Hospital	2201	8 (0.4)	60 (2.7)	27.6 (21.1to 35.6)	15-year: 3.9% (2.8% to 5%)	1953–1997:3.5–8.2
Sweden								
Dong, 2001 *(18)*	1958–2002	Swedish Family-Cancer Database	4650	NA	41 (0.9)	After sem: 11.6 (7.0 to 18.2) After nonsem: 12.4 (7.8 to 18.8)	NA	1958–1997:2.4–5.0

*Studies with at least 1000 patients published in 1990 or later. Syn-CTC = synchronous contralateral testicular cancer; met-CTC = metachronous contralateral testicular cancer; O/E = observed-to-expected ratio; CI = confidence interval; sem = seminoma; nonsem = nonseminoma; NA = not available.

†Numbers in parentheses represent crude percentages.

‡Incidence figures per 100 000 persons *(2–9)*.

§For whites only, based on data in the Surveillance, Epidemiology, and End Results (SEER) Program *(59)*.

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